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Review

The relationship between prescribed pre-operative knee-extensor exercise dosage and effect on knee-extensor strength prior to and following total knee arthroplasty: a systematic review and meta-regression analysis of randomized controlled trials

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SUMMARY

Objective: The aim of this systematic review was to evaluate the relationship between prescribed knee-extensor strength exercise dosage in pre-operative exercise intervention and the effect on knee-extensor muscle strength prior to and following TKA. Additional meta-analyses report the effect of pre-habilitation on outcomes prior to and following TKA.
Design: A systematic literature search was performed including RCT's evaluating the effect of pre-operative exercise prior to and following TKA. Meta-regression analysis was performed to evaluate the dose-response relationship between prescribed exercise dose and the pooled effect, measured as standardized mean difference (SMD). The prescribed exercise dose was quantified using a formula accounting for as many exercise descriptors as possible. Risk of bias in the included trials was assessed using the Cochrane *Risk of Bias Tool*.
Results: Twelve trials with 616 patients were included. Meta-regression analysis showed no relationship between prescribed pre-operative knee-extensor exercise dosage and change in knee-extensor strength neither prior to (slope 0.0005 [95%CI -0.007 to 0.008]) or 3 months following TKA (slope 0.0014 [95%CI -0.006 to 0.009]). Prior to TKA, a moderate effect favoring pre-operative exercise for increase in knee-extensor strength was found (SMD 0.50 [95%CI 0.12 to 0.88]), but not at 3 months following TKA (SMD -0.01 [95%CI -0.45 to 0.43]). Risk of bias was generally assessed as unclear.
Conclusion: Meta-regression analysis of existing trials suggests no relationship between the prescribed pre-operative knee-extensor exercise dosage and the change in knee-extensor strength observed prior to and following TKA. Pre-operative exercise including knee-extensor muscle strength exercise increased knee-extensor strength moderately prior to but not 3 months following TKA.
Protocol registration: PROSPERO ID (CRD42018076308) (http://www.crd.york.ac.uk/PROSPERO/).

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Introduction

Patients diagnosed with knee osteoarthritis (OA) report knee pain, decreased physical function and quality of life[1]. Physically, patients with knee OA are characterized by low knee-extensor muscle strength which is associated with decreased physical function, independent of knee pain[2]. Further, patients diagnosed with severe knee OA awaiting total knee arthroplasty (TKA) have 35% lower knee-extensor muscle strength compared to age-matched controls[3]. Additionally, 60–80% of their pre-operative knee-extensor muscle strength is lost shortly (days to weeks) after surgery, likely due to arthrogenic muscle inhibition[4–6].

Pre-habilitation is defined as an intervention (e.g., exercise therapy) aiming to improve the physical capacity of a patient prior to a stressful event (e.g., surgery), so that the patient can better withstand the negative consequences of surgery[7,8]. Pre-habilitation may also have a positive effect on knee OA symptoms and support patient's self-management of their knee OA condition – potentially postponing the need for surgery[9,10]. Considering the population of patients awaiting TKA, we see two arguments for pre-habilitation: 1) The recovery challenges following TKA include low knee-extensor muscle strength, knee pain, low physical function and long time-to-recovery[11,12]. This may make pre-habilitation important for optimization of physical function in patients awaiting TKA and may enhance recovery after surgery[12–14]. 2) When assessing the need for surgical or non-surgical treatment, information on changes in symptoms during pre-habilitation is valuable in the shared decision-making process when deciding on surgery or not[7,15].

Systematic reviews published within the last 15 years on the effect of pre-habilitation on post-operative outcomes in patients undergoing TKA have found only moderate-to-small or no clinically relevant improvements in knee pain, performance-based function and muscle strength outcomes[16–25]. Despite a potential for efficacy of pre-habilitation in patients eligible for TKA there is a scarcity of robust dose-response evidence[26]. Recent trials by Calatayud *et al.* and Skoffer *et al.* investigating pre-habilitation prior to TKA found clinically relevant effects prior to and following TKA on knee-extensor muscle strength, knee pain and physical function outcomes[27,28]. The trials by Calatayud *et al.* and Skoffer *et al.* differ from previous trials by prescribing large pre-habilitation exercise dosages targeting the knee-extensor muscles with a clear reporting of the exercise intensity (repetitions relative to 1 repetition maximum (RM))[27,28]. The most recent systematic review included the trials by Calatayud *et al.* and Skoffer *et al.* in their meta-analysis[22]. However, the potential larger effect in these trials, due to larger exercise dosages, could be overlooked in a meta-analysis, blurring a potential dose-response relationship. This calls for an analysis of the dose-response relationship between the size of the prescribed pre-habilitation knee-extensor exercise dosage and change in outcomes in patients awaiting TKA.

Objectives

The aim of this systematic review was to evaluate the dose-response relationship between prescribed knee-extensor muscle strength exercise dosage in pre-habilitation and the effect on knee-extensor muscle strength (primary outcome), performance-based function and patient-reported outcomes (secondary outcomes) prior to (primary end-point) and following TKA (secondary end-point) in patients with severe knee OA. Additional meta-analyses report the effect of pre-habilitation on outcomes prior to and following TKA.

We hypothesized that a positive relationship (higher exercise dosage correlates with a larger increase) exists between prescribed knee-extensor muscle strength exercise dosage and increase in knee-extensor strength, performance-based function and patient-reported outcomes in patients prior to and following TKA.

Methods

Protocol and registration

The systematic review was conducted in accordance with the guidelines in the Cochrane Handbook[29]. The protocol was pre-registered on PROSPERO (CRD42018076308) 4/1-2018. The protocol followed the PRISMA-P guideline[30] and the review is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline[31].

Eligibility criteria

Randomized controlled trials (RCT's) with the following characteristics were included: Patients scheduled for TKA diagnosed with knee OA according to the American College of Rheumatology criteria[32] and radiographic verified knee OA classified as Kellgren–Lawrence classification $\geq$2. The exercise intervention was "resistance training" as defined in the Medline Medical subject Heading (MeSH) database "*A type of strength-building exercise program that requires the body muscle to exert a force against some form of resistance, such as weight, stretch bands, water, or immovable objects. Resistance exercise is a combination of static and dynamic contractions involving shortening and lengthening of skeletal muscles*"[33] and had to take place prior to surgery, i.e., pre-habilitation. The exercise intervention had to comprise at least one strengthening exercise primarily targeting the knee-extensor muscles (e.g., sitting knee-extension). The control groups should either be described as receiving: a lower exercise dosage than the intervention group, exercise not defined as resistance training, no intervention, "care as usual", placebo control or patient education. All included trials had to have an assessment of knee-extensor muscle strength and to have an outcome assessment prior to surgery. Trials with follow-up outcome assessments after surgery were also included to assess whether effects following pre-habilitation improved outcomes following TKA (secondary analysis). No limitation in follow-up time was applied.

Information sources and search

A systematic literature search was performed 27/8-2019 in the following databases; Medline via PubMed, Embase via OVID, CINAHL via EBSCO, and CENTRAL. The literature search included medical subject headings (e.g., MeSH in PubMed) and text words related to "knee OA" and "exercise therapy". The PEDro database was also searched. To further ensure literature saturation, we scanned the reference lists of the included trials for relevant references and performed forward reference searching in Web of Science. Only trials reported in English, Danish, Norwegian, Swedish, German or Dutch were included. Language, however, was not a limitation in the search and no limit on date was applied. The search strategy was created by RSH, CJ and TB and performed by RSH. The search string for Medline is available in supplementary material 1. This search strategy was adapted to the other databases. To limit the search to RCTs, the *Cochrane Highly Sensitive Search Strategy for identifying randomized trials* was applied.

Study selection

All identified titles and abstracts were assessed for eligibility by two independent reviewers (RSH and TB) based on the inclusion and exclusion criteria. All trials judged eligible by at least one reviewer were obtained in full text and assessed in detail according to the eligibility criteria by the same two reviewers. In case of disagreement on eligibility, a third researcher was consulted (MSR).

Data collection process

Double data-extraction was applied with RSH and MSR independently extracting the pre-defined data (see below data items). The extracted data was entered the online software program covidence.org and cross-checked for differences in data-extraction. We contacted the corresponding author of Walls *et al.*[34] regarding access to raw data as the published data was only presented in figures. We received no response and, thus, we extracted data from the figures using the WebPlotDigitizer freeware.

Data items

The following data items were extracted from the included trials: *Trial-related data:* Year of publication, authors, design, registration (prospectively or not), follow-up time-points and number of patients allocated to intervention and control group. *Patient-related data:* Sex, age, body mass index (BMI), baseline level of knee pain and radiographic severity of knee OA. *Intervention-related data:* Type and number of knee-extensor exercises, length of intervention (weeks), number of exercise sessions per week, number of sets per exercise session, number of repetitions per set, intensity of the exercise (repetition maximum (RM/% of 1 RM)) and a description of other exercises in the intervention. The Consensus on Exercise Reporting Template (CERT)[35] was used as the template for data extraction of exercise related data, and supplemented by the mechanobiological exercise descriptors suggested by Toigo and Boutellier[36]. For this systematic review prescribed exercise volume was investigated, not the actual completion of exercise (adherence). *Control group data:* A brief description of the intervention. *Outcome-related data:* Primary outcome; knee-extensor strength (e.g., isometric or isokinetic measurements) which is a valid (0.78–0.92) and reliable (inter-trial 0.98–1.00, inter-evaluator 0.92–0.99) measure of change in knee-extensor strength in the TKA population[37]. Secondary outcomes; knee pain, patient reported physical function (e.g., activities of daily living), knee-related performance-based function (e.g., ability to climb stairs) and adverse events.

Risk of bias in individual trials

The risk of bias in the included trials was assessed using the Cochrane *Risk of Bias Tool*[38]. The assessment was completed independently by two reviewers (RSH and TB). No cases of disagreement occurred and the third reviewer (MSR) was not needed as an arbitrator. Each of the following domains was evaluated as to whether they were adequate (low risk of bias), unclear or inadequate (high risk of bias); sequence generation, allocation concealment, blinding of participants, personnel and outcome assessor, incomplete outcome data, selective outcome reporting and other sources of bias.

Primary and secondary analyses

Meta-regression analyses investigating the effect of prescribed pre-operative knee-extensor exercise dosage on knee-extensor strength, knee pain, patient reported physical function and knee-related performance-based function prior to and 3 months following TKA was performed. The primary analysis was the relationship between prescribed pre-operative knee-extensor exercise dosage and effect on knee-extensor strength prior to TKA. All other meta-regression analyses were considered secondary. Previous investigations have examined the influence of some important exercise dosage descriptors (e.g., number of weeks or sessions) on knee pain and physical function in patients with mild-to-severe knee OA[39–41]. However, when investigating single exercise descriptors there is a risk of leaving out important information related to the total exercise dosage prescribed[42]. To account for as many relevant exercise dosage descriptors as possible, as described by Toigo and Boutellier and Slade *et al.*[35,36], we defined knee-extensor exercise dosage as:

$$Knee-extensor\ \ exercise\ \ dosage = (knee * w * s * se * r) * \frac{i}{r}$$

Abbreviation explanation: knee = number of knee-extensor exercises, w = weeks, s = sessions per week, se = sets per session, r = repetitions per set, i = exercise intensity (estimated % 1 RM).

In trials where the exercise intensity was not reported (10 of 12 included trials) the number of repetitions was used to estimate the exercise intensity, according to the Holten curve (e.g., 11 repetitions = exercise intensity corresponding to 11 RM = 80% of 1 RM)[43]. The *total number of repetitions* (knee*w*s*se*r) was multiplied with the *exercise intensity* divided by *repetitions per set* (i/r) to normalize the exercise dosage to the 1 RM scale/the Holten curve[43].

Additional analyses

Effect sizes for continuous data are presented as standardized mean differences (SMD) with 95% confidence intervals (CI) and prediction intervals. The standardized mean difference (SMD) was estimated as the difference between final scores in the intervention and control groups divided by the pooled standard deviation (SD), allowing pooling and comparison of outcomes across the individual trials according to the Cochrane Collaboration[29]. The mean scores and SD's were extracted where available or otherwise calculated from CI's or standard errors (SE)[29] (dataset and code available in supplementary material 6 and 7). The effect size of the SMD was interpreted as following; 0.2 = small, 0.5 = moderate and >0.8 = large (Cohen's d)[44]. All effect sizes were adjusted with the Hedges bias correction to Hedges g[29].

Synthesis of results

Between-trial inconsistency was assessed using I^2 statistics, where 30–60% were defined as moderate heterogeneity. All outcomes were combined and analyzed using Stata statistical software version 11.0 and followed the statistical guidelines from the Cochrane Collaboration[29]. If tests of heterogeneity were <30% the fixed effect model was used. If statistical heterogeneity was observed (I^2 >30%) the random effects model was chosen.

Risk of bias across trials

In case of small trials with a large effect (risk of small study bias), we conducted a funnel plot, Eggers regression test and the "trim and fill" method to investigate this. The results of the meta-analyses are presented in forest-plots. In case of high levels of heterogeneity (I^2 >30%) between the results in the included trials, trial characteristics are analyzed by meta-regression to investigating the impact on the heterogeneity (reduction in tau-squared (T^2)).

Results

Study selection

After removing duplicates, 4550 potentially relevant articles were identified. Following title and abstract screening, 4510 articles were excluded, and 40 articles were read full text. Twenty-eight articles were excluded as they did not meet the inclusion criteria and 12 articles were included for analysis (Fig. 1).

Trial characteristics

Data were extracted for 616 patients scheduled for TKA (median (range), age 65.9 (62.1–70.7), BMI 31.0 (27.9–34.8), 58.6% female). Four of the 12 included trials were prospectively registered[28,45–47] while the remaining eight trials did not provide information on registration[27,34,48–53]. Five trials provided 'no pre-habilitation'/'care-as-usual' in the control group[28,48,51–53], three provided 'patient education/information'[46,47,50], three provided 'other lower extremities exercises'[27,34,45], and one trial provided 'exercises for the upper extremities'[49]. The pre-habilitation interventions included on average 1.8 knee-extensor exercises (range 1–3), an average duration of 6 weeks (range 4–8.9), an average of 4.4 sessions/week (range 2–14), 2.5 knee-extensor sets/session (range 1.5–3.5) and 11 repetitions/set (range 8–15). Two trials clearly reported the exercise intensity according to the 1 RM principle[27,28]. The pre-habilitation intervention was performed as supervised group sessions for all trials[27,28,45–53] except one (home-based)[34] (Table I). In four trials the supervised group sessions were supplemented with home-based exercise programs[45,51–53] (Table I).

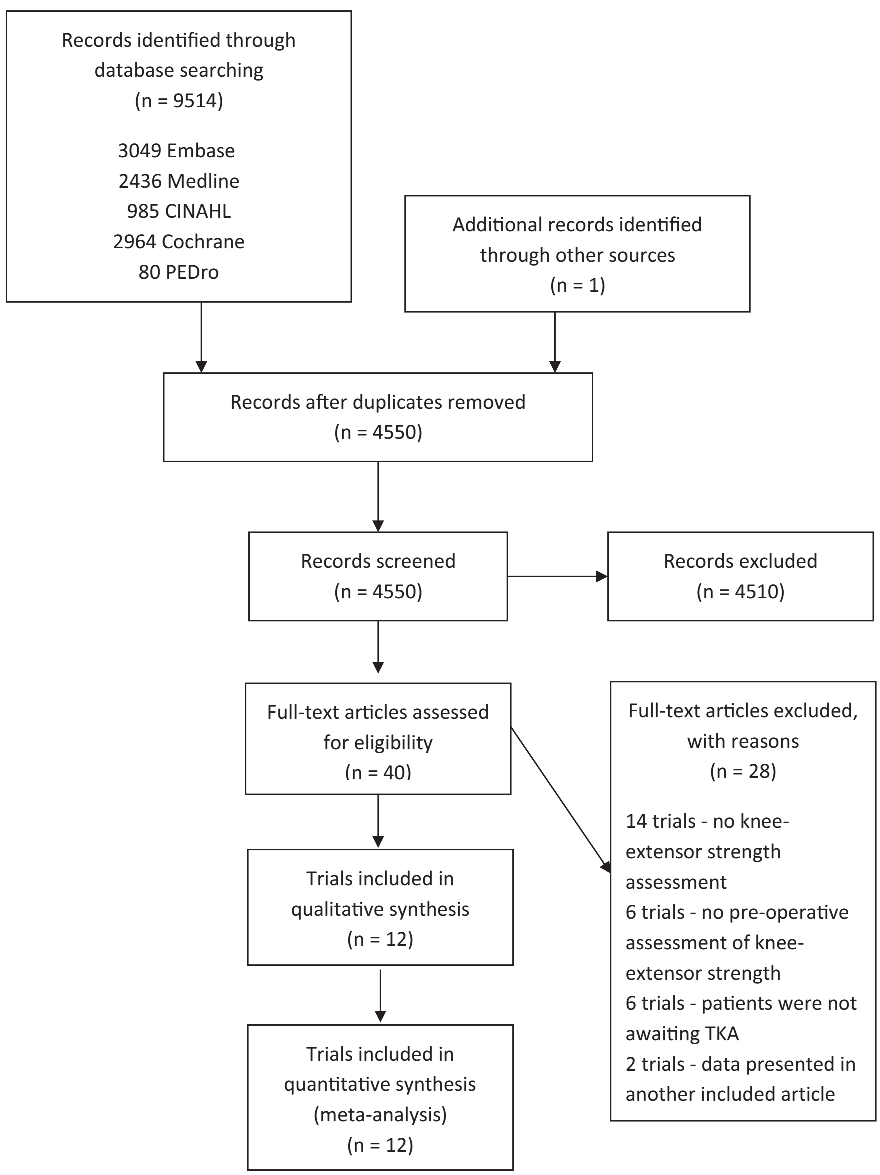

Fig. 1 Flowchart of included trials, presented in accordance with the PRISMA 2009 guidelines[31]. Twelve trials were included in the final qualitative synthesis and quantitative analysis. RCT = randomized controlled trial, OA = osteoarthritis, TKA = total knee arthroplasty.

Author, year, trial design and registration	Patient characteristics (intervention group)	Patient characteristics (control group)	Pre-habilitation intervention (intervention group)	Prescribed pre-habilitation knee-extensor exercise dosage*	Pre-habilitation intervention (control group)	Outcome measures†	End-points‡
Weidenhielm 1993[51] RCT, not prospectively registered	n: 19 Age: 64 (4) BMI (kg/m^2): 30.1 % women: 57.9 Knee pain (no pain, mild pain, moderate pain, severe pain): 0, 1, 10, 8	n: 20 Age: 63 (5) BMI (kg/m^2): 29.1 % women: 45.0 Knee pain (no pain, mild pain, moderate pain, severe pain): 0, 2, 13, 5	Knee-extensor exercises: - Seated knee-extension with ankle weights Other exercises: - Warming up on bicycle - Knee mobility exercises - Strengthening exercises for the whole limb Supervised exercise provided by a physiotherapist	Knee-extensor exercises: 1 Weeks: 5 Sessions/week: 7 (3 supervised session and the patients were recommended to practice the same program at home every day) Sets/session: 2 Repetitions/set: 10 Intensity/repetition (% RM): Not reported. Estimated: 10 RM Knee-extensor exercise dosage: 56.0	No pre-habilitation provided	Knee-extensor strength: Isokinetically at 30°/s (Cybex II dynamometer)	Prior to TKA 3 months following TKA
Börjesson 1996[53] RCT, not prospectively registered	n: 34 Age: 64 (4) BMI (kg/m^2): 28.4 % women: 50.0 Knee pain: Na	n: 34 Age: 64 (5) BMI (kg/m^2): 27.7 % women: 50.0 Knee pain: Na	Knee-extensor exercises: - Seated knee-extension with ankle weights Other exercises: - Knee mobility exercises - Strengthening exercises for the lower limb Supervised exercise provided by a physiotherapist	Knee-extensor exercises: 1 Weeks: 5 Sessions/week: 5 (3 supervised and 2 at home) Sets/session: 2 Repetitions/set: 10 Intensity/repetition (% RM): Not reported. Estimated: 10 RM Knee-extensor exercise dosage: 40.0	No pre-habilitation provided	Knee-extensor strength: Isokinetically at 30°/s (Cybex II dynamometer)	Prior to TKA
Beaupre 2004[48] RCT, not prospectively registered	n: 65 Age: 67 (7) BMI (kg/m^2): 32.0 (6.0) % women: 60.0 WOMAC pain: 49.0 (15.0)	n: 66 Age: 67 (6) BMI (kg/m^2): 31.0 (5.0) % women: 50.0 WOMAC pain: 49.0 (20.0)	Knee-extensor exercises: - Static quadriceps contraction - Short arc quadriceps contraction - Isotonic quadriceps contraction in sitting from 90° to zero degrees Other exercises: - Warmup: Hot pack applied to the involved knee - Low resistance cycling. - Hamstring contraction in sitting using tubing for resistance. - Straight leg raise to an approximate angle of 45° - Cool-down: Ice pack applied to the involved knee Supervised exercise provided by a physiotherapist	Knee-extensor exercises: 3 Weeks: 4 Sessions/week: 3 Sets/session: 3 Repetitions/set: 12.5 (avg.) Intensity/repetition (% RM): Not reported. Estimated: 12.5 RM Knee-extensor exercise dosage: 86.4	No pre-habilitation provided	Knee-extensor strength: Isometric (hand-held dynamometer) PROM: WOMAC pain WOMAC stiffness WOMAC function	Prior to TKA 3 months following TKA
Rooks 2006[50] RCT, not prospectively registered	n: 22 Age: 65 (8) BMI (kg/m^2): 35.7 (9.2) % women: 50.0 WOMAC pain: 7.0 (2.0)	n: 23 Age: 69 (8) BMI (kg/m^2): 33.9 (6.5) % women: 57.0 WOMAC pain: 6.5 (4.5)	Knee-extensor exercises: - Leg-press Other exercises: - Three weeks water-based exercise prior to land-based exercise - Seated row - Chest press - Biceps curls - Triceps kickback - Movements for the abdomen and shoulders - Flexibility exercises for hips, knees and ankles flexors and extensors and hip adductors Supervised exercise provided by a physiotherapist Knee-extensor exercises:	Knee-extensor exercises: 1 Weeks: 3 Sessions/week: 3 Sets/session: 2 Repetitions/set: 10 Intensity/repetition (% RM): Not reported. Estimated: 10 RM Knee-extensor exercise dosage: 14.4	Information from pre-operative education booklet	Knee-extensor strength: 1-repetition maximum leg-press PROM: WOMAC pain WOMAC function Function: Timed “Up & Go”	Prior to TKA

Table I (*continued*)

Author, year, trial design and registration	Patient characteristics (intervention group)	Patient characteristics (control group)	Pre-habilitation intervention (intervention group)	Prescribed pre-habilitation knee-extensor exercise dosage*	Pre-habilitation intervention (control group)	Outcome measures†	End-points‡
Walls 2010[34] Pilot RCT, not prospectively registered	n: 5 Age: 63.2 (11.4) BMI (kg/m^2): 32.8 (6.3) % women: 80.0 WOMAC pain: 10.0 (5.7)	n: 9 Age: 64.4 (8.0) BMI (kg/m^2): 30.7 (3.0) % women: 50.0 WOMAC pain: 11.7 (2.7)	- Five second hold static quadriceps strengthening exercise in supine - Five second hold static quadriceps strengthening exercise in supine with cushion roll under the knee Other exercises: - Straight leg raises - Knee flexion and extensions exercises performed both sitting and, if tolerated, in standing Unsupervised exercise	Knee-extensor exercises: 2 Weeks: 8 Sessions/week: 14 (twice daily) Sets/session: 1 (not reported Repetitions/set: 15 (avg.) Intensity/repetition (% RM): Not reported. Estimated: 15 RM Knee-extensor exercise dosage: 168.0	Isometric quadriceps strengthening exercise in sitting with toe against the wall (knee joint in 60° flexion) with neuromuscular electrical stimulation on the quadriceps muscle for 20 min a day on alternate days for the first 2 weeks and then every day for the next 6 weeks	Knee-extensor strength: Isometric (Biodex dynamometer) PROM: WOMAC pain WOMAC: stiffness WOMAC function Function: Stair climbing test	Prior to TKA 3 months following TKA
Swank 2011[52] RCT, not prospectively registered	n: 36 Age: 63.1 (7.3) BMI (kg/m^2): 35.9 (8.5) % women: 66.7 Knee pain: Na	n: 35 Age: 62.2 (7.6) BMI (kg/m^2): 32.9 (5.7) % women: 62.9 Knee pain: Na	Knee-extensor exercises: - Squat - Seated knee-extension with elastic exercise bands Other exercises: - 5-min warm-up consisting of light walking - Hip flexion - Hip extension - Hip abduction - Hip adduction - Ankle plantar flexion - Ankle dorsal flexion - Knee flexion - A series of forward and lateral step training exercises up and down a standard 8-inch step - Cool-down session of light static stretching followed by 5 min of light walking Supervised exercise provided by research personnel	Knee-extensor exercises: 2 Weeks: 5.5 (range 4−8) Sessions/week: 3 (1 supervised and 2 at home) Sets/session: 1.5 (avg.) Repetitions/set: 10 Intensity/repetition (% RM): Not reported. Estimated: 10 RM Knee-extensor exercise dosage: 39.6	No pre-habilitation provided	Knee-extensor strength: Isokinetically at 60°/s (Biodex 3 dynamometer) Function: Stair climbing test	Prior to TKA
McKay 2012[49] Pilot RCT, not prospectively registered	n: 10 Age: 63.5 (4.9) BMI (kg/m^2): 35.0 (6.1) % women: 50.0 WOMAC pain: 10.1 (2.2)	n: 12 Age: 60.6 (8.1) BMI (kg/m^2): 33.8 (7.1) % women: 66.7 WOMAC pain: 11.9 (3.6)	Knee-extensor exercises: - Seated leg-press - Seated knee-extension Other exercises: - 10-min aerobic warm-up (treadmill, cycling ergometer, rowing ergometer, or recumbent stepper) - Standing calf raise - Leg curl Supervised exercise provided by a kinesiologist	Knee-extensor exercises: 2 Weeks: 6 Sessions/week: 3 Sets/session: 2 Repetitions/set: 8 Intensity/repetition (% RM): Not reported. Estimated: 8 RM Knee-extensor exercise dosage: 61.2	Placebo exercise program, upper body exercises: - 10-min aerobic warm-up (treadmill, cycling ergometer, rowing ergometer, or recumbent stepper) - Seated latissimus dorsi [lat] pull, chest press, elbow flexion, elbow extension	Knee-extensor strength: Isometric at 75° knee flexion (leg-extension machine with a force meter attached to the lever arm) PROM: WOMAC pain WOMAC function Function: Stair climbing test 50-foot walk test	Prior to TKA 3 months following TKA
van Leeuwen 2014[45] Pilot RCT, prospectively registered	n: 10 Age: 71.8 (7.5) BMI (kg/m^2): 27.9 (4.6) % women: 30.0 Knee pain: Na	n: 8 Age: 69.5 (7.1) BMI (kg/m^2): 27.9 (3.1) % women: 50.0 Knee pain: Na	Knee-extensor exercises: - Seated knee-extension (1-leg) - Seated leg-press (1 leg). - Squat Other exercises: - Step-up (1-leg) - Therapy included information and advice, exercise of activities of daily life, training of walking with aids, maintenance of mobility, and aerobic training (walking, cycling) Supervised exercise provided by a physiotherapist	Knee-extensor exercises: 3 Weeks: 6 Sessions/week: 5 (2−3 supervised and 2−3 at home) Sets/session: 3.5 (avg.) Repetitions/set: 11 (avg.) Intensity/repetition (% RM): Not reported in RM. Estimated: 11 RM Knee-extensor exercise dosage: 252.0	Therapy included information and advice, exercise of activities of daily life, training of walking with aids, maintenance of mobility, and aerobic training (walking, cycling), but the patients in this group were not allowed to perform resistance training	Knee-extensor strength: Isometric at 75° knee flexion (custom-made dynamometer) Function: Stair climbing test Six-minute walk test	Prior to TKA 3 months following TKA
Villadsen 2014[46] RCT,	n: 41 Age: 67.1 (8.8) BMI (kg/m^2):	n: 40 Age: 65.1 (9.0) BMI (kg/m^2):	Knee-extensor exercises: - Seated knee-extension with elastic exercise bands	Knee-extensor exercises: 1 Weeks: 8	Basic education package/care as usual (written information on the operating procedure,	Knee-extensor strength: Isometric at 75°	Prior to TKA 3 months

(continued on next page)

Table I (*continued*)

Author, year, trial design and registration	Patient characteristics (intervention group)	Patient characteristics (control group)	Pre-habilitation intervention (intervention group)	Prescribed pre-habilitation knee-extensor exercise dosage*	Pre-habilitation intervention (control group)	Outcome measures†	End-points‡
prospectively registered	30.8 (4.9) % women: 61.0 KOOS pain: 47.8 (14.9)	33.4 (5.8) % women: 60.0 KOOS pain: 39.7 (12.6)	Other exercises: - 10 min warm-up on ergometer cycle - Pelvic lift - Sit-ups - Slide-exercise forward-backward/forward lunge - Slide-exercise sideways/sideway lunge - Abduction with elastic exercise band - Adduction with elastic exercise band - Knee flexion with elastic exercise band - Chair stand - Step up and down a step-board - Cool-down - Basic education package (same as control group) Supervised exercise provided by a physiotherapist	Sessions/week: 2 Sets/session: 2.5 (avg.) Repetitions/set: 12.5 (avg.) Intensity/repetition (% RM): Not reported. Estimated: 12.5 RM Knee-extensor exercise dosage: 32.0	expected postoperative progress, and a leaflet on various exercises normally given when scheduled for total knee replacement)	knee flexion (custom-made dynamometer) PROM: KOOS pain KOOS adl function KOOS symptoms KOOS sport and recreation KOOS quality of life Function: 20-m walk test	following TKA
Huber 2015[47] RCT, prospectively registered	n: 22 Age: 68.8 (8.0) BMI (kg/m^2): 30.8 (4.9) % women: 50.0 KOOS pain: 48.1 (17.6)	n: 23 Age: 71.9 (8.1) BMI (kg/m^2): 29.9 (5.5) % women: 43.5 KOOS pain: 47.3 (16.8)	Knee-extensor exercises: - Seated knee-extension with elastic exercise bands Other exercises: - Ergometer cycling for 10 min - Pelvic lift - Sit-ups - Slide-exercise forward-backward/forward lunge - Slide-exercise sideways/sideway lunge - Hip abductors/hip adductors with elastic band - Knee flexors with elastic band - Chair stands - Stair climbing - Mobility and stretching exercises - Cooling down (walking) - Knee School x 3 Supervised exercise provided by a physiotherapist	Knee-extensor exercises: 1 Weeks: 8.9 Sessions/week: 2 Sets/session: 2.5 (avg.) Repetitions/set: 12.5 (avg.) Intensity/repetition (% RM): Not reported. Estimated: 12.5 RM Knee-extensor exercise dosage: 35.6	3 x Knee School: The knee school was taught by an experienced and specially-trained physiotherapist over 3 individual or group sessions, one session per week, starting about 4 weeks before the operation. Knee school sessions were separately organised for participants of the intervention group and those of the control group to avoid contamination. The content of the knee school included information on anatomy of the knee joint and adjacent functional structures, recommended activities with prosthesis and post-operative pain management, and details on the post-operative rehabilitation phase. Didactical elements included models of the knee joint and the lower extremity, working sheets, photos and videos, handouts, PowerPoint presentations and peer discussions	Knee-extensor strength: Isometric (hand-held pull gauge) PROM: KOOS pain KOOS adl function KOOS symptoms KOOS sport and recreation KOOS quality of life Function: Timed “Up & Go” 20-m walk test	Prior to TKA 3 months following TKA
Calatayud 2016[27] RCT, not prospectively registered	n: 30 Age: 70.7 (7.3) BMI (kg/m^2): 32.0 (4.2) % women: Na WOMAC pain: 10.5 (0.9)	n: 29 Age: 70.1 (6.4) BMI (kg/m^2): 31.0 (3.8) % women: Na WOMAC pain: 10.6 (0.9)	Knee-extensor exercises: - Seated knee-extension - Seated leg-press Other exercises: - 15-min warm-up consisting of dynamic joint movements performed without ballistic movements and dynamic body weight exercises including 2 sets of 20 repetitions of step-ups and calf raises at a platform and finally 10 min of light-intensity hand or leg ergometry cycling (depending on the perceived pain)	Knee-extensor exercises: 2 Weeks: 8 Sessions/week: 3 Sets/session: 5 Repetitions/set: 10 Intensity/repetition (% RM): 10 RM Knee-extensor exercise dosage:192.0	Not reported in published paper. Information provided via e-mail correspondence with the corresponding author. Below is an excerpt from the e-mail correspondence: “Before TKA, the control (usual care) did not receive any supervised intervention without any follow-up. Patients were just advised to perform three different isometric exercises everyday: (1) knee extension during 6–10 s while seated on a chair or table, 10–20 sets, 10–20	Knee-extensor strength: Isometric (hand-held dynamometer) PROM: WOMAC pain WOMAC: stiffness WOMAC function Function: Timed “Up & Go” Stair climbing test	Prior to TKA 3 months following TKA

Table I (*continued*)

Author, year, trial design and registration	Patient characteristics (intervention group)	Patient characteristics (control group)	Pre-habilitation intervention (intervention group)	Prescribed pre-habilitation knee-extensor exercise dosage*	Pre-habilitation intervention (control group)	Outcome measures†	End-points‡
			- A single warm-up set was also performed before each resistance training exercise by using a light resistance for 10 repetitions - Leg curl - Hip abduction - After completing the strengthening exercises, participants performed 4 sets of 30 s of double leg stance and 4 sets of 15 s of single leg stance on the same unstable device (Bosu) - 5-min cool-down of light static stretching of hip abductors, flexors and extensors of the knee and ankle plantar flexors Supervised exercise provided by a physiotherapist		times/day; (2) hip flexion during 5–10 s while lying on mat with knee fully extended, 10–30 repetitions; (3) knee extension during 6–10 s while seated with legs extended horizontally on a mat, with a rolled towel under the knees, 10–20 sets, 10–20 times/day."		
Skoffer 2016[28] RCT, prospectively registered	n: 30 Age: 70.7 (7.3) BMI (kg/m^2) median (range): 30.0 (22.6–42.5) % women: 63.3 KOOS pain: 53.0 (13.3)	n: 29 Age: 70.1 (6.4) BMI (kg/m^2) median (range): 31.8 (24.3–42.2) % women: 58.6 KOOS pain: 53.4 (13.5)	Knee-extensor exercises: - Seated knee-extension - Seated leg-press Other exercises: - 10-min warm-up on a stationary bike - Knee flexio - Hip extension - Hip abduction - Hip adduction - 3 × 30 s of stretching of knee extensors, knee flexors and ankle flexors Supervised exercise provided by a physiotherapist	Knee-extensor exercises: 2 Weeks: 4 Sessions/week: 3 Sets/session: 3 Repetitions/set: 10 Intensity/repetition (% RM): 10 RM Knee-extensor exercise dosage:57.6	No pre-habilitation provided	Knee-extensor strength: Isometric at 70° knee flexion (isokinetic dynamometer) PROM: KOOS pain KOOS adl function KOOS symptoms KOOS sport and recreation KOOS quality of life Function: Timed "Up & Go" Six-minute walk test	Prior to TKA 3 months following TKA

Data is presented as mean (SD). RCT = randomized trial. BMI = Body mass index. KL = Kellgren-Lawrence scale. PROM = Patient reported outcome measure. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. KOOS = Knee osteoarthritis outcome score. Na = Not available. Prescribed pre-habilitation knee-extensor exercise dosage = (number of knee-extensor exercises*weeks*sessions/week*sets/sessions*repetitions/set)*exercise intensity/repetitions per set. When the exercise intensity was not provided the number of repetitions was used instead and the intensity is given as equivalent to this in % 1RM.

* Exercises intensity estimated from number of repetitions and the Holten curve 42.

† Data extracted for present review.

‡ End-points used for the present review.

Table I Characteristics of included trials

Risk of bias within trials

None of the included trials performed adequate blinding of patients and physiotherapists towards the intervention[54,55]. "Selective outcome reporting" was assessed as unclear in eight of the trials as we could not locate a published trial protocol or registration. Three trials were assessed as high risk of bias as not all pre-specified outcomes from the trial-registration were reported[28,45,47]. One trial was assessed as high risk bias under the domain "other sources of bias" as there was no reporting of the intervention in the control group[27] - information on this has later been provided via e-mail correspondence with the corresponding author (Table I). Generally, the included trials lacked information on methods to reduce risk of bias and many were assessed as unclear (Fig. 2).

Dose-response

Meta-regression analysis showed no relationship between prescribed pre-habilitation knee-extensor exercise dosage and knee-extensor strength prior to (slope 0.0005 [95% CI -0.007 to 0.008]) (Fig. 3) or at 3 months following TKA (slope 0.0014 [95% CI -0.006 to 0.009]). No relationship was found between prescribed knee-extensor dosage and knee pain or physical function neither prior to nor 3 months following TKA (Supplementary material 2). Due to an insufficient number of trials recommended for meta-regression analyses (<5 trials) the secondary meta-regression analyses for stair climbing test, Timed "Up & Go", short distance walk test and 6-min walk test were not conducted[56,57].

	Weidenhielm 1993	Börjesson 1996	Beaupre 2004	Rooks 2006	Walls 2010	Swank 2011	McKay 2012	van Leeuwen 2014	Villadsen 2014b	Huber 2015	Calatayud 2016	Skoffer 2016
Sequence generation	?	?	?	?	+	?	?	+	?	+	+	?
Allocation concealment	?	?	?	?	?	?	?	-	+	+	+	?
Blinding of participants and personnel	?	?	?	?	?	?	?	-	?	?	?	-
Blinding of outcome assessor	?	?	?	?	+	?	?	+	+	+	?	+
Incomplete outcome data	+	+	+	-	+	+	+	-	+	+	+	-
Selective outcome reporting	?	?	?	?	?	?	?	-	+	-	?	-
Other sources of bias	?	?	?	?	?	?	?	?	+	+	-	+

Fig. 2 Risk of bias within trials assessed with the Cochrane ***Risk of Bias Tool***[38]. Each of the domains was evaluated as to whether they were adequate (green) (low risk of bias), unclear (yellow) or inadequate (red) (high risk of bias).

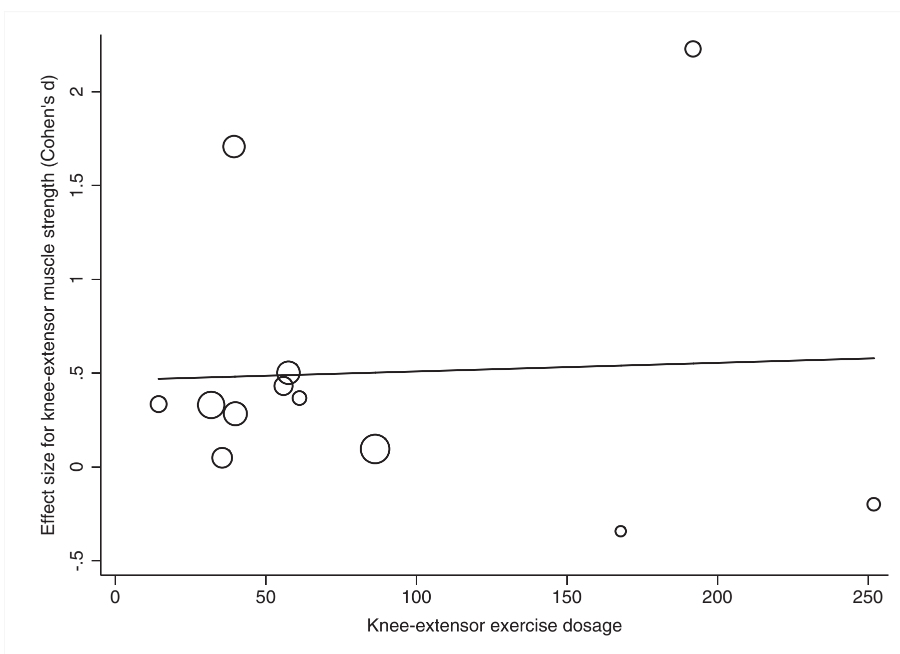

Fig. 3 Unadjusted meta-regression analysis on the relationship of prescribed knee-extensor exercise dosage and pre-operative muscle strength. On the y-axis the effect size (SMD) of the dependent variable pre-operative knee-extensor strength is displayed. On the x-axis the independent variable is displayed, prescribed pre-habilitation knee-extensor exercise dosage: (number of knee-extensor exercises*weeks*sessions/week-*sets/sessions*repetitions/set)*exercise intensity/repetitions per set. The full black line shows the slope of the relationship between the prescribed knee-extensor exercise dosage and effect-size on muscle strength. The individual trials are shown by circles and the weight of the individual trials is shown by the size of the circles (i.e., larger circles indicate larger weight).

Pre-operative effects of pre-habilitation

Twelve trials reported the effect of pre-habilitation on pre-operative knee-extensor strength[27,28,34,45–53]. Overall, a moderate effect favoring pre-habilitation for an increase in knee-extensor strength prior to TKA was found (SMD 0.50 [95% CI 0.12 to 0.88]), with substantial heterogeneity ($I^2 = 78.5\%$) (Fig. 4). For the secondary outcomes, pre-habilitation did not significantly improve knee pain, patient reported physical function, stair climbing test, Timed "Up & Go", short distance walking (15–25 m) or 6-min walk test prior to TKA (Fig. 5). Large heterogeneity ($I^2 > 30\%$) was present in all meta-analyses and a random effects model was performed. Meta-analyses stratified by comparator are available in supplementary material 3 and estimated prediction intervals in supplementary material 8.

Post-operative effects of pre-habilitation

Nine trials reported the effect of pre-habilitation on 3 months post-operative knee-extensor strength[27,28,34,45–49,51]. Overall, we found no effect of pre-habilitation on knee-extensor strength 3 months following TKA (SMD -0.01 [95% CI -0.45 to 0.43]) (Supplementary material 4), with substantial heterogeneity ($I^2 = 77.3\%$). No effect of pre-habilitation was seen in any post-operative outcomes (Fig. 6). Meta-analyses stratified by comparator are available in supplementary material 3 and estimated prediction intervals in supplementary material 8.

Risk of small study bias and exploring heterogeneity

The funnel plot did not show clear asymmetry (Supplementary material 5) and Eggers regression test showed no indication of small-study effects. The meta-analysis on pre-operative knee-extensor strength showed a between-study variance ($Tau^2 = 0.3394$). The between-study variance was reduced using meta-regression analysis adjusted for sex expressed as percentage women in individual trials ($Tau^2 = 0.126$) (slope 0.0540 [95% CI 0.016–0.0915]). Thus, with a 10% increase of women in the study, the SMD for knee-extensor muscle strength would increase by 0.5.

Discussion

In this meta-regression analysis of 12 trials, including more than 600 patients, no relationship was found between prescribed pre-operative knee-extensor exercise dosage and the effect on knee-extensor muscle strength neither prior to- nor 3 months following TKA. The additional meta-analyses showed that pre-habilitation, including knee-extensor resistance training in patients eligible for TKA, was associated with a moderate increase in knee-extensor muscle strength prior to surgery but not 3 months following TKA. When interpreting the results, the risk of bias must be considered as most of the included trials lacked sufficient information on important methodology such as sequence generation, allocation concealment and blinding of participants and personnel.

Dose-response

Contrary to our hypothesis, we did not find a positive dose-response relationship between prescribed pre-habilitation knee-extensor exercise dosage and change in knee-extensor strength or any secondary outcomes. A potential explanation for the lack of a positive dose-response relationship could be the assumptions that we had to make when calculating the prescribed exercise dosage. Assumptions about intensity was made as the

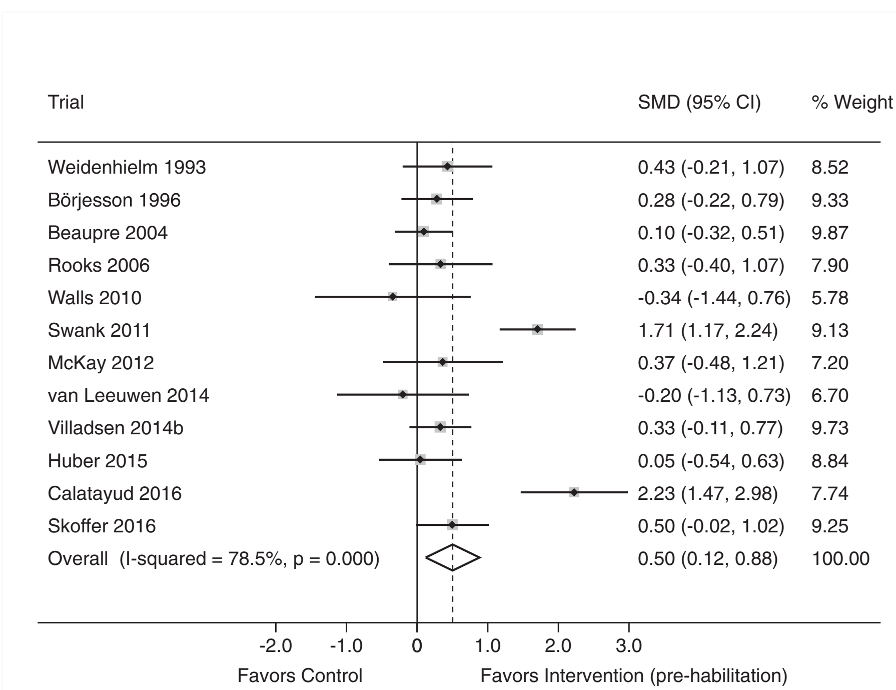

Fig. 4 Forest plot of the effect of pre-habilitation including knee-extensor exercise on pre-operative knee-extensor muscle strength. SMD = standardized mean difference. Individual trial and total effect are shown with 95% confidence intervals ((SMD (95% CI)). Weights are from a random effect analysis.

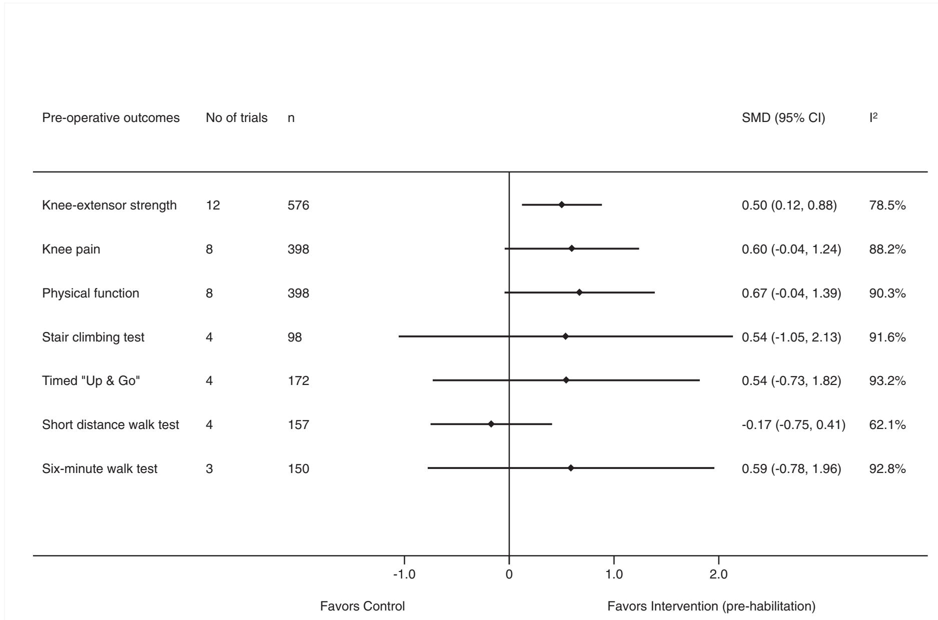

Fig. 5 Forest plot of pooled effect sizes for all pre-operative outcomes. SMD = Standardized mean difference. Total effects are shown with 95% confidence intervals ((SMD (95% CI)). I^2 = heterogeneity.

exercise dosage descriptors were insufficiently reported in the included trials. We found it imperative to include the exercise intensity in the exercise dosage-calculation as the physiological response to resistance training is highly dependent on the intensity[42]. However, ten of the included twelve trials did not, or did not clearly, report the prescribed exercise intensity relative to 1RM. We requested this information from the corresponding authors during the data collection process. One author provided the information, three did not have it available and six did not reply to the request. As a consequence of this missing information and to refrain from subjective estimation of the exercise intensity based on information provided in the trials, we chose an approach of estimating the exercise intensity based on the number of repetitions by use of the Holten curve[43]. Though not optimal, we consider this the most objective and transparent approach to include exercise intensity in the dosage-calculation. We analyzed the prescribed exercise dosage and not the actual exercise completed (adherence) which could also explain the lack of a positive dose-response relationship.

Generally, this challenge of inadequate intervention reporting is a well-recognized challenge in non-pharmacological interventions[58], not least in the reporting of exercise program details for patients with knee OA[59,60]. This creates challenges for many types of users of the published research, including clinicians, researches and patients. More importantly is that clinicians and patients are not able to reproduce safe and effective interventions[60]. Together this calls for better reporting of exercise characteristics by using templates such as the TIDieR (Template for Intervention Description and Replication)[61] and CERT checklists[35] and the mechanobiological exercise descriptors outlined by Toigo and Boutellier[36]. Further, only four of the included twelve trials had a pre-registered and publicly available trial protocol summary, and none had a public available full trial protocol. The processes of trial pre-registration and protocol publication could contribute to more detailed description of exercise interventions as trial protocol guidelines would refer to the above mentioned templates for reporting exercise characteristics[62,63].

Another potential explanation for the lack of a positive dose-response relationship is that patients eligible for TKA can achieve an increase in their knee-extensor muscle strength by exercising at lower intensities. This would be supported by the result from the present meta-regression analysis. Patients eligible for TKA are not very physically active due to limitations related to their knee condition[64,65]. Inactive lifestyle leads to decrease in muscle strength and physical ability, especially in older adults[66–68] leaving a large potential for improvement[42]. Potentially, patients eligible for TKA do not need to exercise with high intensity to achieve muscle strength improvements[69]. As an example, in untrained healthy individuals loads of 45–50% of 1 RM have been shown to increase muscle strength[42]. Given an average exercise intervention length of 6 weeks, we expect neural adaptions more than adaptions in muscle morphology[43]. However, the forest-plot of the effect of pre-habilitation prior to TKA on knee-extensor strength (Fig. 4) also show that not all trials found an effect on knee-extensor strength.

Future research should focus on pre-registered, randomized dose-response trials in patients potentially eligible for TKA with clear exercise reporting and assessment of adherence[70–72].

Pre-operative effects of pre-habilitation

When evaluating the effects of pre-habilitation prior to surgery in patients eligible for TKA, the importance of focusing on knee-extensor muscle strength is supported by the result of the present

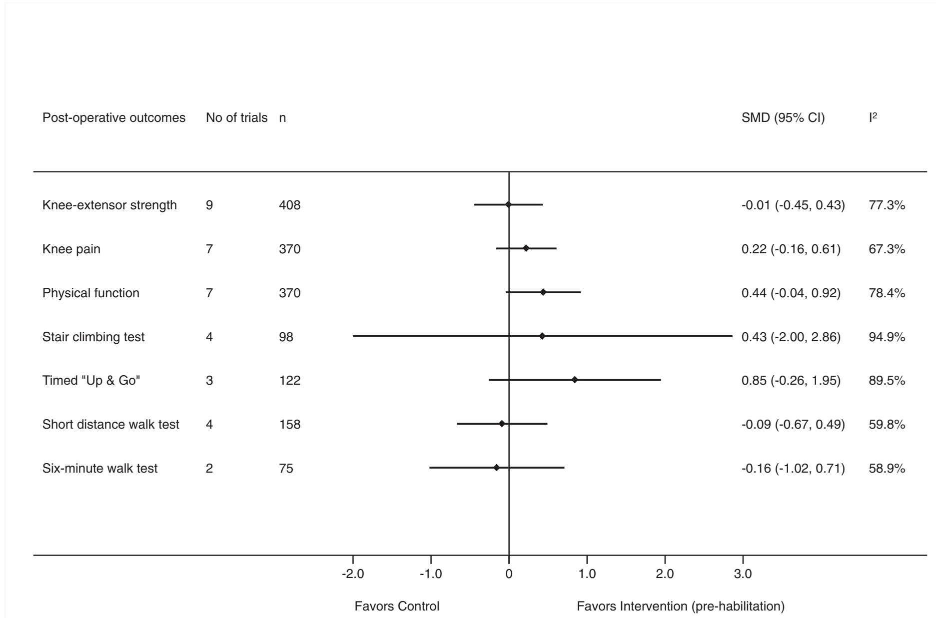

Fig. 6 Forest plot of pooled effect sizes for all 3 months post-operative outcomes. SMD = Standardized mean difference. Total effects are shown with 95% confidence intervals ((SMD (95% CI)). I^2 = heterogeneity.

Osteoarthritis and Cartilage

meta-analysis showing a moderate increase in knee-extensor muscle strength. The secondary outcomes knee pain and physical function changed in a positive direction favoring the intervention, though not statistically significant. Pre-operative improvements in knee pain and physical function has previously been reported in patients eligible for TKA following exercise therapy[10]. The lack of significant effect on knee pain and physical function could be explained by insufficient increase in knee-extensor muscle strength (16.2%). As an example, a 30–40% increase in knee-extensor strength has been suggested to be needed for improving knee pain and disability[73].

Post-operative effect of pre-habilitation

The effects of pre-habilitation prior to TKA were not seen 3 months following TKA and contradict the hypothesis that pre-operative changes also improve post-surgical knee-extensor strength. Thus, the potential of pre-habilitation to enhance post-operative rehabilitation does not seem likely, though there was a trend for improved physical function 3 months following TKA. A possible explanation for this, is that effects gained from pre-operative exercise is attenuated by the physiological stress induced by the surgical procedure of TKA, e.g., inhibiting neuromuscular function[6].

Legitimacy of pre-habilitation in patients eligible for TKA

The lack of a clinical relevant effect of pre-habilitation following TKA, found in this review and previous[16–25], questions the premise “Better in – better out” underlying the concept of “pre-habilitation” in TKA[8]. It seems more appropriate to refer patients eligible for TKA to rehabilitation with the purpose of improving knee OA related symptoms and not to “prepare” the patient for surgery, even though the patients fulfill the criteria for surgery. In line with this, a combined analysis of two trials showed that patients eligible for TKA experience clinical relevant changes following exercise therapy and 66% delay surgery for at least 2 years[10]. Another approach to “pre-habilitation” would be using it in shared decision-making when discussing the option of surgery[15]. As an example, a care pathway for a patient eligible for TKA could be outlined as follows: 1) assessment of symptoms and treatment options, 2) referral to exercise therapy and 3) re-assessment of symptoms and treatment options (e.g., surgery). We suggest changing the focus from “pre-habilitation” – including pre-operative exercise to enhance post-operative recovery – to “pre-evaluation” – including pre-operative exercise to enhance shared surgical decision-making – in an enhanced recovery program after TKA. A patient eligible for TKA who has had no improvement in knee related symptoms following pre-operative exercise could be scheduled for surgery, while a patient with satisfactory improvements could continue non-surgical treatment.

Strengths and limitations

This is the first dose-response analysis on pre-habilitation in patients eligible for TKA to account for several exercise dosage descriptors including exercise intensity. Sufficient information was not available to calculate an exact exercise dosage and the approach we used to estimate exercise intensity could have introduced bias. A limitation of this review is that we analyzed prescribed – and not completed – exercise, as exercise adherence data were not available. However, this reflects clinical practice where valid adherence information is difficult to obtain[74–77]. Further, in eleven of the included twelve trials the exercise interventions were described as supervised, however no data was provided on how much control there was on completion of the prescribed exercise dosage.

Conclusions

Meta-regression analysis of existing trials suggests no relationship between the prescribed pre-operative knee-extensor exercise dosage and the change in knee-extensor strength observed prior to and following TKA. Pre-operative exercise including knee-extensor muscle strength exercise increased knee-extensor strength moderately prior to but not 3 months following TKA. No effect was found for any secondary outcomes.

Author contribution

Conception and design: Husted, Juhl, Rathleff and Bandholm.
Data acquisition: Husted, Rathleff and Bandholm.
Analysis and interpretation of the data: All authors.
Drafting of the article: Husted.
Critical revision of the article for important intellectual content: All authors.
Statistical expertise: Juhl.
Final approval of the article: All authors. Mr. Husted (rasmus.skov.husted@regionh.dk) and Prof. Bandholm (thomas.quaade.bandholm@regionh.dk) takes responsibility for the integrity of the work as a whole.

Competing interests statement

None of the authors have competing interests in relation to this work.

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Role of the funding sources

The funding sources had no role in this work.

Supplementary data

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